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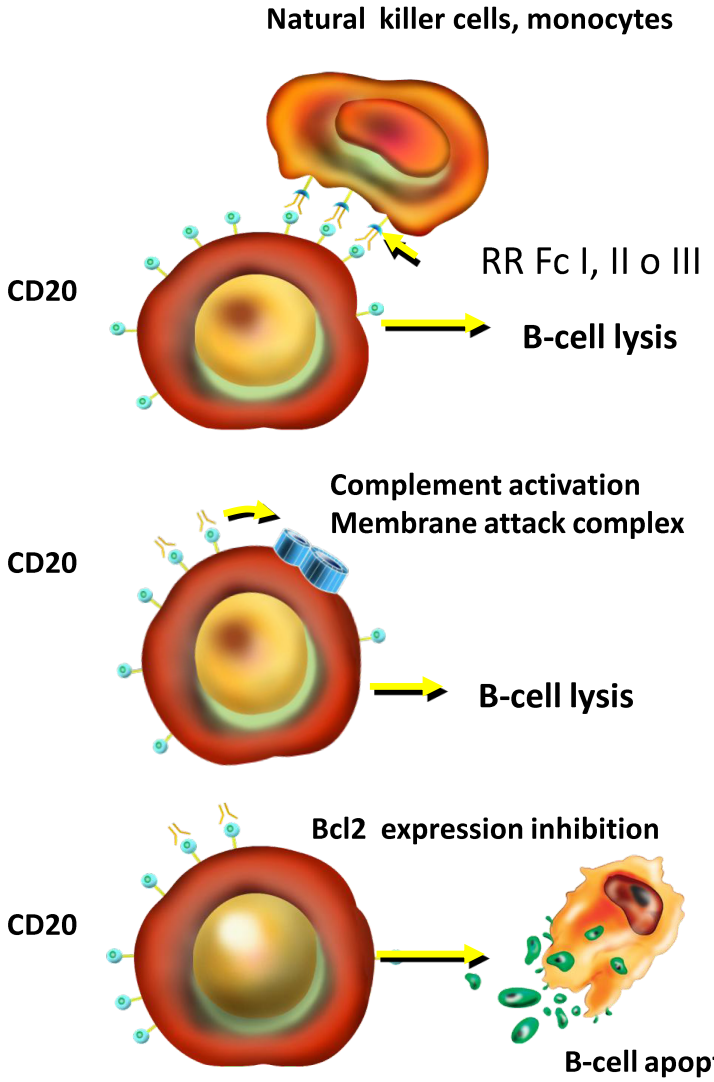

Figure 2: Upon binding to its receptor, rituximab induces B-cell depletion through three different mechanisms: (a) antibody-dependent cytotoxicity, (b) complement-mediated cell lysis and (c) induction of apoptosis.

Discussion

Rituximab in membranous glomerulonephritis

The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

Membranous nephropathy (MN) is an antibody-mediated renal disease characterized by the deposition of subepithelial immune complexes in the glomerular capillary. Several clinical and experimental data indi-cate that B cells are a key element in the pathogenesis of MN[3,4]. Inhibi-tion of B-cell function reduces pro-teinuria in experimental models of several MN, and in the same line[5], clinical studies[6] have clearly shown that the inhibition of B cells by treatment with alkylating agents induces remission of nephrotic syndrome. In recent years, the availability of rituximab has allowed analysis of the effect of a more selective inhibition of B cells in primary MN. To date, various studies have analysed the efficacy of rituximab as first-line treatment in patients with intolerance or resistance to previous treatments or with dependence of calcineurin inhibitors. Overall, the available evidence is limited to observational studies[7–9,10–12] and a systematic review[13], but not randomized clinical trials, comparing the efficacy and safety of rituximab against alkylating agents or calcineurin inhibitors has yet to be reported.

Rituximab as a first-line therapy

The first evidence on the efficacy of rituximab in MN was reported by Remuzzi et al.[7] in a group of eight patients with primary MN and long-standing nephrotic syndrome. Following the administration of one dose of 375 mg/m^2 rituximab weekly for four consecutive weeks, there was a reduction in proteinuria. After a 20-week follow-up, the percentage of patients in complete or partial remission of nephrotic syndrome (62.5%) was only slightly lower than that reported with alkylating agents and calcineurin inhibitors (70–80%). The reduction of proteinuria was associated with depletion of circulating B cells, which was evident after the first dose and maintained throughout the observation period of 20 weeks. In a second article[8], the same group described the 12-month follow-up of eight patients treated with the same regimen. The reduction in proteinuria was quantitatively higher in the first 3 months after treatment and persisted throughout the study period with a percentage of total or partial remissions of 50% at 12 months. These studies provided the first clinical data on the efficacy of rituximab in MN but also showed that not all patients respond to treatment. In 2006, Ruggenenti et al.[9] analysed the possible predictors of response

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in a small group of patients with MN treated with rituximab and noted an inverse association between reduction of proteinuria and interstitial fibrosis and tubular atrophy. The first studies published prescribed a treatment regimen based on that described for B-cell lymphoma, consisting in the administration of one dose of 375 mg/m^2 rituximab per week for four consecutive weeks. In 2004, data from the treatment of rheumatoid arthritis[14] suggested a different dosing schedule for autoimmune diseases, comprising the administration of two doses of 1 g, separated by an interval of 15 days. Cravedi et al. in 2006[10] compared the efficacy of the classical protocol of four doses with an alternative schedule, in which after the initial dose subsequent doses were administered according to the number of circulating CD19 cells. These authors reported that the administration of rituximab guided by the number of circulating B cells was as effective as the classic pattern and had the advantage of avoiding unnecessary re-exposure to the drug while reducing the cost of treatment. One area of great interest is the pharmacokinetics of rituximab in nephrotic syndrome. Since rituximab is a 231 amino acid phosphoprotein with a molecular weight of 145 Kd, urinary losses of rituximab could limit its efficacy during the acute nephrotic phase. Fervenza et al.[11] conducted an interesting study in which they treated 15 patients suffering from MN with two doses of 1 g rituximab administered at an interval of 15 days and incorporated a pharmacokinetic analysis. At 12 months, the percentage of total or partial remissions (57.1%) was similar to those described in previous studies. Although the mean proteinuria at the time the first dose administered was 9.8 g/day, depletion of circulating CD19 cells was observed in all patients. Moreover, although the levels of CD19 in patients with MN recovered before a control group of patients with rheumatoid arthritis (without nephrotic syndrome), there was no difference in rituximab levels between patients with and without response at any time, which suggests that urinary losses of rituximab do not reduce its effectiveness. All studies discussed so far focused initially on the efficacy of rituximab in inducing remission of proteinuria, without studying other morphological or functional parameters. In 2008, Ruggenenti et al.[12] analysed the effect of treatment with rituximab in different morphofunctional parameters in a study including seven patients with MN that underwent repeated kidney biopsy. These authors reported that 21 months after treatment, there was a significant increase in fractional sodium clearance, a decrease of renal plasma flow and an increase in renal vascular resistance. Repeated biopsies showed significant reduction or disappearance of subepithelial deposits in association with a reduction in IgG4 deposition and with an increase in the number of electron-dense filtration diaphragms. Overall, they concluded that the morphofunctional changes observed after the disappearance of proteinuria could have a renoprotective meaning (Table 1a).

Rituximab associated to calcineurin inhibitors

The likelihood of remission in patients with MN treated with calcineurin inhibitors depends on the total duration of treatment. Treatment periods of 6 months induce remissions in approximately 60% of patients while when treatment is prolonged between 12 and 18 months, the probability of complete or partial remission averages 80%. Moreover, the incidence of recurrence of nephrotic syndrome after withdrawal of calcineurin inhibitors observed in different studies is high and ranges over 60%. Recurrences require reintroduction of calcineurin inhibitors for periods of time, which in some patients can

Table 1 Rituximab in idiopathic membranous nephropathy
1a Rituximab as a first-line therapy

Reference	*n*	Response (%)	Total remission (%)	Partial remission (%)	No response (%)	Follow-up (months)
Remuzzi et al.[7]	8	5 (62.5)	2 (25)	3 (37.5)	3 (37.5)	20
Ruggenenti et al.[8]	68	47 (69.1)	NA	NA	21 (30.8)	12
Ruggenenti et al.[9]	14	8 (57.1)	NA	NA	6 (42.8)	3
Cravedi et al.[10]	12	8 (66)	2 (17)	6 (50)	4 (33)	12
Fervenza et al.[11]	14	8 (57.1)	2 (14.2)	6 (42.8)	6 (42.8)	6–12
Ruggenenti et al.[12]	7	7 (100)	NA	NA	0	7–59
Ruggenenti et al.[19]	68	47 (69)	NA	NA	21 (31)	6
TOTAL	191	130 (68)*				3–59

* Response includes both complete and partial remissions.

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be very long. Two pilot studies have analysed whether the use of rituximab in combination with calcineurin inhibitors can shorten the treatment period required to obtain remission and/or obtain stable remissions of proteinuria after the withdrawal of calcineurin inhibitors. Regarding the first aspect, a recent controlled non-randomized clinical trial[15] analysed whether the association of rituximab with tacrolimus could induce earlier and more stable remissions of proteinuria than monotherapy with tacrolimus in patients with primary MN. The study included 18 consecutive patients with primary MN and normal renal function with nephrotic syndrome lasting for more than 6 months despite treatment with angiotensin II blockers. All patients started treatment with tacrolimus monotherapy at doses of 0.06 mg/kg/day, which was subsequently adjusted to maintain through levels within 7–9 ng/ml. During the first 6 months after tacrolimus, all patients were treated with one dose of 375 mg/m^2 of rituximab/week for four consecutive weeks. After administration of the last dose of rituximab, tacrolimus dose was reduced by 30% per month until either discontinuation of treatment or evidence of relapse. The probability of response at each time period was compared with a cohort of 36 patients treated with tacrolimus monotherapy or in association with steroids. The results of this study indicate that the association of tacrolimus to rituximab is associated with a significantly lower proteinuria at 9 months after initiation of treatment, can prevent recurrence after suppressing calcineurin inhibitors and increases the number of patients that remain in remission with no treatment at 12 and 18 months. Though promising, these data should be the subject of rigorous evaluation in randomized studies before attempting to move them to clinical practice. A second study[16] provided new data demonstrating the utility of rituximab to overcome the dependence of calcineurin inhibitors. This study included adult patients with idiopathic membranous GM who were in full or partial remission but had a long history of relapses and clear criteria for dependence on calcineurin inhibitors. Following administration of one cycle of four doses of rituximab, it was possible to remove the calcineurin inhibitors in all cases. During follow-up, the recovery of B cells was not associated with recurrence of nephrotic syndrome. Three patients had late recurrences long time after administration of the first treatment cycle, and in all of them, remission was achieved with the administration of a single dose of 1 g of rituximab. After extended follow-up, all patients remained in remission without calcineurin inhibitors (Table 1b).

Rituximab in patients resistant to standard therapies

There is also limited, low-level evidence indicating that rituximab could be useful in patients with MN resistant to conventional therapies. Fervenza et al.[17] have recently extended the experience with rituximab in a study including 20 patients (11 of which had failures to prior therapy). All patients received retreatment at 6 months regardless of proteinuria response. Of 18 patients who completed 24 months follow-up, 4 were in complete remission, 12 were in partial, 1 had a limited response and 1 patient relapsed.

Similar observations were reported by Cravedi et al.[18] in a matched cohort study comparing 2-year outcomes of 11 consecutive patients with primary MN who received rituximab for persisting nephrotic syndrome or relapsing disease. Finally, a recent observational study, which included 100 patients with MN treated with rituximab, described a frequency of partial or total remissions of 65%, whether rituximab was indicated as first-line treatment or is administered after prior exposure to other immunosuppressants[19].

In summary, the current data, albeit with low level of evidence, are homogeneous and indicate that rituximab may have a role in the treatment of membranous glomerulonephritis. However, there is not enough data to define the indications against alkylating agents or calcineurin inhibitors. A multicentre randomized control study comparing the use of rituximab versus cyclosporine in the treatment of MN has recently been finished (ClinicalTrials.gov Identifier: NCT01180036) and will provide valuable information on this subject. Moreover, despite the growing demonstration of positive responses to rituximab in MN, the evidence that this disease tends to have a chronic clinical course with intercurrent outbreaks of activity raises doubts about the ability of this drug to modify the long-term clinical course, especially taking into account that the re-exposure to rituximab can induce the formation of neutralizing antibodies that limit their effectiveness. For the

1b Rituximab associated to calcineurin inhibitors

Reference	*n*	Responders	Total response (%)	Partial response	No response	Follow-up months
Segarra et al.*[16]	13	13	13 (100)	—	—	6–30

* Results after 30 months of follow-up.

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time being, it seems rational to consider treatment with rituximab in patients who do not respond or have contraindications to conventional treatment regimens and in patients who have developed dependence to calcineurin inhibitors. The mechanisms by which rituximab can induce remission of nephrotic syndrome in MN are not known. It seems logical to assume that its main effect should be explained by a reduction of the synthesis of antibodies and/or the interference with the function of B-lymphocyte and antigen-presenting cell, secondary to depletion of circulating B cells; however, there is some evidence that the explanation would not be so simple. First, after treatment with rituximab, B-cell depletion occurs in all patients while only 60–70% of them show total or partial response[7,8,11]. Second, recovery of circulating B cells is not associated with a recurrence of nephrotic syndrome[8,9,11,16]. Finally, in the studies reported by Remuzzi et al.[7] and Ruggenenti et al.[8], although the maximum effect on proteinuria was seen within the first 1–3 months after treatment, proteinuria continued to decline after the sixth month when, in some patients, there was a recovery in the number of circulating CD19 cells (Table 1c).

Rituximab in minimal change nephropathy

Minimal change nephropathy (MCN) is characterized by the absence of proliferation of the cellular elements intrinsic to the glomerulus, the absence of cellular infiltration by external elements and the absence of immune deposits. The only structural alteration seen is the effacement of podocyte foot processes seen by the electron microscope. The cause (or causes) of podocyte injury has been the subject of numerous studies and is today still a matter of debate[20]. The favourable response of nephrotic syndrome to immunosuppressant agents has been considered as an undeniable proof of the involvement of the immune system. Most of the evidences indicate an important role of T cells in the pathogenesis of MCN[20,21]. However, the report of an unexpected resolution of the nephrotic syndrome in a patient treated with rituximab for a B-cell lymphoproliferative disorder[22] led to rethink the role of B cells in the pathogenesis of MCN. Since then, several case reports and small series of patients have confirmed the evidence of remission of nephrotic syndrome with rituximab in both adults and child patients with minimal change disease (MCD). So far, the evidence is limited to cases in which the indication has been steroid resistance, the occurrence of multiple relapses, dependence or intolerance to classic drugs such as corticosteroids and calcineurin inhibitors. The reported evidence[23–38] is summarized in Tables 2a and 2b. In patients with steroid and/or CNI dependence, rituximab can reduce the number of relapses and induce sustained remissions in about 70% of cases, but 25% of patients will require retreatment to maintain remission. The available data for steroid-resistant patients are scarce and limited to case reports[27,28,32] and an uncontrolled study including 16 patients[54]. Overall, the results indicate that about half of the patients may have complete or partial remission after treatment with rituximab but relapse occurs in 50% of them. The absence of clinical trials comparing the efficacy of rituximab against other therapeutic options prevents conclusions about what should be its specific indications. As in the case of MN, rituximab should be considered as a therapeutic option for patients with multiple recurrences that develop dependence to calcineurin inhibitors and for difficult-to-treat patients who are resistant to first- and second-line treatments (steroids, calcineurin inhibitors and alkylating agents).

Rituximab in primary focal and segmental glomerulosclerosis (FSGS)

The rationale to indicate rituximab treatment in FSGS is based on the hypothesis that the podocyte injury is caused by an inmunomodulable, B-cell–related, pathogenic mechanism[39]. However, recent evidence indicates that rituximab could reduce proteinuria for having direct effects on intracellular signalling pathways and podocyte cytoskeleton architecture[40]. There are isolated case reports and observational studies on the efficacy of rituximab in patients with FSGS[41–48]. The results are discordant as regards to the effect both on proteinuria and on renal function. Thus, the available evidence is not enough to ascertain whether rituximab should or should not be indicated in patients with steroid-resistant FSGS. The results of individual case reports suggest that there might be a better response to rituximab in children than in adults, but this point

1c Rituximab in patients resistant to standard therapies

Reference	*n*	Responders (%)	Total response (%)	Partial response (%)	No response (%)	Follow-up months
Fervenza et al.[17]	18	16 (88)	4 (22.2%)	12 (66.6%)	2 (12)	24
Ruggenenti et al.[19]	32	18 (56.25)	NA	NA	14 (43.7)	6–60
TOTAL	50	34 (68)	—		16 (32)	—

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Table 2 Rituximab in minimal change nephropathy
2a Rituximab in steroid dependence and multiple recurrences

Reference	*n*	Indication	Associated treatment	Rtx dose	Response	Relapse	Retreatment	Follow-up months
Benz et al.[23]	1	Steroid dependence and recurrence	CsA, Ig IV	Four doses of 375 mg/m^2	1 CR	0	No	13
Gilbert et al.[24]	1	Steroid dependence	Steroids Tacrolimus	Four doses of 375 mg/m^2	1 CR	0	One, two doses	18
François et al.[25]	1	Multiple recurrences	Steroids	Four doses of 375 mg/m^2	1 CR	1	One, Two doses at 12 months	28
Smith[26]	1	Multiple recurrences	Steroids Tacrolimus	One dose of 375 mg/m^2	1 CR	0	No	9
Peters et al.[33]	1	Dependence on steroids and CNI	ND	Two doses of 1,000 mg at 2 weeks	1 RC	1	1, 2 dose 1000 mg at 2 weeks	NA
Yang et al.[29]	1	Multiple relapses	MMF Steroids	Four doses of 375 mg/m^2	1 CR	0	No	12
Sawara et al.[31]	1	Multiple relapses	Steroids	One dose of 500 mg	1 CR	0	NA	NA
Garjau et al.[34]	11	Contraindication to steroids and dependence to calcineurin inhibitors	NA	Four doses of 375 mg/m^2	11 CR	0	No	6–24
Kisner et al.[37]	3	Steroid dependence	Pred-nisone, calcineurin inhibitors and MMF	Two doses of 1 g	1 CR at 3 months	0	NA	3–25
Munyentwali et al.[48]	17	Multiple recurrences and dependence	Multiple therapies	Four doses of 375 mg/m^2 for 15 patients and 1 g for two patients	11 CR	6	No	5, 1–82
Fujinaga et al.[55]	10	Dependence and recurrence	CsA, MMF or MZR	Four doses of 375 mg/m^2	9 CR	1	No	13–21
Sellier-Leclere et al.[56]	30	Steroid dependence	Multiple therapies	375/m^2 one dose for two patients, two doses for 10 patients, three doses for three patients, four doses for 15 pa-tients	19 CR	11	10	15–24
TOTAL	78	—	—	—	58 (74.3%)	20 (25.6%)	13 (16.6%)	3–28

CR, complete remission; CsA cyclosporine; Ig, high-dose immunoglobulins, MZR, mizoribine; MMF, mycophenolate mofetil.

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2b Rituximab in steroid-resistant patients								
Reference	*n*	Indication	Associated treatment	Rtx dose	Response	Relapse	Retreatment	Follow-up months
Hofstra et al.[27]	1	Resistant nephrotic syndrome	MMF Steroids Tacrolimus	Two doses of 1,000 mg	1 PR	No	No	4
Bagga et al.[28]	2	Steroid and CsA resistance	IgS CyA	Four doses of 375 g/m^2	1 CR or 1 PR		No	4–14
Kurosu et al.[32]	2	Steroid resistance	NA	One dose of 375 mg/m^2	2 PR	No	Second dose at 6 months	12
Gulati et al.[54]	16	Steroid resistance	Prednisone and calcineurin inhibitors	Four doses of 375 mg/m^2	5 CR OR PR	11	NA	6–12
TOTAL	21				10 (47.61%)	11 (53.59%)		4–14

has not been adequately analysed. Although the results are also discordant, treatment with rituximab, usually associated with plasmapheresis, has been associated with greater apparent success in treating the post-transplant recurrence of FSGS when compared with FSGS of the native kidney[44,45]. However, the data observed in post-transplant recurrence cannot be extrapolated to primary FGS of native kidney for several reasons. First, since recurrence is only seen in approximately 30% of patients, it could be associated with a particular pathogenic mechanism, which may be different than those causing podocyte injury in nonrecurrent forms. Second, in transplant patients, relapse is evident in a background of combined strong immunosuppression, so the mechanisms responsible for recurrence appear to be quite insensitive to immunomodulation. Finally, post-transplant recurrence is usually diagnosed by the evidence of proteinuria, which in several cases could even not reach the nephrotic range[44–46]. Therefore, it is possible that the treatment of relapsing forms is initiated in earlier stages of podocyte injury and therefore most likely to respond to therapeutical measures (Table 3).

Rituximab for steroid-dependent idiopathic nephrotic syndrome

Recent studies[47–51,52–54] analysed the effectiveness of rituximab in patients with steroid-dependent idiopathic nephrotic syndrome. These studies, however, included patients with different renal diseases (MCD, FSGS, mesangial hypercellullarity and patients in whom biopsy data were not available), and in all cases, results are described for the whole group but not detailed for each particular renal disease. This is the reason why these studies are described separately. The results of observational studies[49–51,52–54] are similar to those described in patients with steroid-dependent MCN and are summarized in Table 4. Overall, data from these studies indicate that approximately 80% of patients with steroid dependence can maintain remission after treatment with rituximab. Most patients, however, suffer one or more relapses and need to be retreated. In the long term, 40–50% of patients can maintain remission with no other immunosuppressive therapy. The efficacy of rituximab versus other drugs in preventing relapses in patients with steroid dependence has been investigated in two studies—an observational trial[50] and a randomized clinical trial[53]. In the first one[50], the number of relapses observed in patients treated with three to four repeated doses of rituximab was comparable with that observed in a control group of patients treated with tacrolimus for 12 months[50]. In the only clinical trial carried out to date in patients dependent on corticosteroids and calcineurin inhibitors[53], 54 children were randomized to continue with standard therapy versus rituximab associated to low doses of steroids and calcineurin inhibitors. At 3 months, proteinuria was lower in the rituximab arm as compared with standard therapy. The relapse rates were lower, and the probabilities of being drug free at 3 and 9 months was significantly higher in the rituximab group. These results indicate that rituximab and lower doses of prednisone and calcineurin inhibitors are noninferior to standard therapy in maintaining short-term remission.

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Table 3 Rituximab in primary focal and segmental glomerulosclerosis (FSGS)

Reference	*n*	Indication	Associated treatment	Rtx dose	Responders	Recurrence	Unresponsive	Follow-up months
Suri et al.[45]	1	Steroid resistance and contraindication to CNI	IgG IV	Four dose of 375 mg/m^2	1	0	0	NA
Kaito et al.[46]	1	Steroids, CsA and plasmapheresis resistance	Methylpred-nisolone and CsA	One dose of 375 mg/m^2	1	1	0	8
Fernandez-Fresnedo et al.[47]	8	Steroid-resistant nephrotic syndrome	Immuno-suppressive	Three patients: dose additional Five patients: four dose of 375 mg/m^2	3	1	5	12–24
Kisner et al.[37]	2	Steroid resistance or dependence	Steroids	1 g, two doses	1 CR at 3 months, 1 PR at 3 months	NA	0	3–25
TOTAL	12	—	—	—	7 (58.33%)	2 (16.66%)	5 (41.66%)	3–25

Table 4 Rituximab for steroid-dependent nephrotic syndrome (including minimal change disease and focal glomerulosclerosis)

Reference	*n*	Indication	Associated treatment	Rtx dose	Response	Relapses	Retreatment	Follow-up months
Kamei et al.*[49]	12	Steroid dependent	Steroids, MMF, MZR, TCL, CyA	Single dose of 375/m^2	12	9	7	12
Sinha et al.†[50]	6	Steroid dependence, nephrotic syndrome in children	Steroids	375/m^2 two to three doses	5	5	5	6–18
Sellier-Leclere et al.‡[51]	22	Steroid dependence, nephrotic syndrome in children	Multiple therapies	375 mg/m^2, one to four doses	20	9	18	12–26
Kemper et al.¶[52]	37	Steroid dependence, nephrotic syndrome in children	Steroids	375/m^2, one to four doses	26	24 median time to relapse 9, 6 months	NA	12
Gulati et al.§[54]	24	Steroid dependence and recurrence	Pred-nisone and calcineurin inhibitors	Four doses of 375 mg/m^2	17	6	NA	12–24
TOTAL	94	—	—	—	80 (85, 1%)	53 (54%)	30 (91.8%)	6–26

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Table 4 (*Continued*)

* One patient with FSGS and 11 patients with MCD. Steroids were discontinued in all cases after 74 days. Frequency of relapses per 6 months was significantly reduced and steroid-free period per 6 months was significantly increased after treatment compared with those before treatment.
† Four patients with MCD and two with FSGS and four patients with no biopsy data available. The study compared the frequency of relapses after Rtx or TCL for patients with difficult-to treat steroid-dependent nephrotic syndrome and showed that two or three doses of Rtx were as effective as 12 months treatment with TCL to reduce the frequency of relapses and had an steroid-sparing effect.
‡ Ten patients with MCD, 10 patients with FSGS and 2 patients with no biopsy data. Remission without steroids and calcineurin inhibitors: *n*, 20. Treatment failure, two patients.
¶ No biopsy data available. After the initial rituximab course for >24 months, 7 (24.1%) patients without further maintenance immunosuppression. After repeated rituximab doses, 69% of patients remained on remission and 48% free of associated immunosuppression.
§ Twelve patients with MCD, two patients with FSGS two patients mesangial hypercellularity, eight patients with no biopsy. Remission was sustained in 20 (83.3%) at 12 months and in 17 (71%) at follow-up of 16.8 ± 5.9 months. The mean difference in relapses before and 12 months after treatment with rituximab was 3.9 episodes/patient per year.
MCD, minimal change disease; FSGS, focal and segmental glomerulosclerosis; MMF, mycophenolate; MZR, mizoribine; TCL, tacrolimus; CyA, cyclosporine A.

Conclusion

Rituximab can induce remission of nephrotic syndrome in patients suffering from membranous glomerulonephritis, MCN and focal segmental glomerulosclerosis. The absence of controlled clinical trials comparing rituximab versus standard therapies does not currently allow defining of what should be the specific indication of rituximab in adult primary renal disease. With the current level of evidence, it seems reasonable to consider rituximab as a therapeutic option for patients who have contraindications, intolerance or lack of response to conventional treatment regimens and for patients who depend on calcineurin inhibitors and are at risk of chronic nephrotoxicity.

Abbreviations list

FSGS, focal and segmental glomerulosclerosis; MCD, minimal change disease; MCN, minimal change nephropathy; MN, membranous nephropathy

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